

The Endocannabinoid System: A New Approach to Control Cardiovascular Disease

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The endocannabinoid (EC) system consists of 2 types of G-protein-coupled cannabinoid receptors—cannabinoid type 1 (CB₁) and cannabinoid type 2 (CB₂)—and their natural ligands. The EC system plays a key role in the regulation of food intake and fat accumulation, as well as glucose and lipid metabolism. When overactivated, the EC system triggers dyslipidemia, thrombotic and inflammatory states, and insulin resistance. Blocking CB₁ receptors centrally and peripherally in adipose tissue can help normalize an overactivated EC system. CB₁ blockade helps regulate food intake and adipose tissue metabolism, contributing to improved insulin sensitivity and other features of the metabolic syndrome. Visceral adipose tissue is most closely associated with the metabolic syndrome, which is a constellation of conditions that place people at high risk for coronary artery disease. Targeting the EC system represents a new approach to treating visceral obesity and reducing cardiovascular risk factors. (*Clinical Cornerstone*. 2005;7[2/3]:17–26) Copyright © 2005 Excerpta Medica, Inc.

The endocannabinoid (EC) system is an endogenous and physiologic system that plays a key role in the central and peripheral regulation of energy balance, as well as lipid and glucose metabolism.^{1,2} This system consists of 2 types of G-protein-coupled cannabinoid receptors—cannabinoid type 1 (CB₁) and cannabinoid type 2 (CB₂)—and their natural ligands, ECs such as anandamide. ECs are produced quickly and on demand to activate the CB receptors.^{3,4} CB₁ receptors are located in several areas of the brain, notably the hypothalamus—which is the center of hunger and satiety—and at various peripheral sites, including adipose tissue.⁵ CB₂ receptors are situated throughout the immune system, mainly the spleen, tonsils, mast cells, and thymus as well as the liver and gastrointestinal tract and are involved in immune function.⁶ Significant advances have been made in understanding the complex nature of the EC system within the last decade (**Table**).^{7–22}

ACTIVATION AND OVERACTIVATION

Typically, the EC system is silent and is only activated when the body needs to recover from stressful situations. Thus, the system helps the body to relax by reducing pain and anxiety, as well as modulating body temperature, hormone production, blood pressure, and smooth muscle tone. This system also helps the body to rest (through sedation and inhibition of motor behavior), to forget (via extinction of aversive memories), to protect itself at both the cellular and emotional levels, and to eat (by inducing appetite and reinforcing rewards).^{23,24}

The system is overactivated in animal models of obesity and in response to exogenous stimuli such as excessive caloric intake²⁵ or smoking.²⁶ When overactivated, the EC system triggers dyslipidemia, thrombotic and inflammatory states, and insulin resistance dysglycemia.²⁰

Food intake, and subsequently, lipogenesis, can be manipulated by either blocking or stimulating the EC

TABLE. HISTORICAL DISCOVERY OF THE ENDOCANNABINOID SYSTEM.

1964 – Isolation of Δ^9 -THC, the active constituent of *Cannabis sativa*⁷

1988 – High-affinity cannabinoid-binding site discovered in rat brain⁸

1990 – Cloning of the rat G-protein–coupled cannabinoid receptor type 1 (CB₁) receptor⁹

1991 – Cloning of the human CB₁ receptor¹⁰

1992 – Discovery of anandamide, the first endogenous cannabinoid¹¹

1993 – Cloning of the peripheral cannabinoid type 2 receptor¹²

1994 – Characterization of the first selective CB₁ receptor blocker, rimonabant¹³

1995 – Isolation of a second cannabinoid, 2-arachidonoylglycerol (2-AG), in brain¹⁴

1996 – Activation of CB₁ receptors found to suppress the release of neurotransmitters including acetylcholine, dopamine, serotonin, and GABA¹⁵

1999 – Cannabinoids fail to lower blood pressure in CB₁-knockout mice, implicating CB₁ in this effect¹⁶

2000 – Functional CB₁ receptors found in human vascular endothelial cells¹⁷

2002 – Rimonabant blocks effects of nicotine in rats¹⁸

2003 – Cannabinoids acting on CB₁ receptors found to decrease contractile performance in human atrial muscle.¹⁹ CB₁ knockout in mice leads to leanness, resistance to diet-induced obesity, and enhanced leptin sensitivity²⁰

2004 – Results from rimonabant-focused Phase 3 RIO-LIPIDS, STRATUS-US, RIO-Europe studies offer a novel approach to cardiovascular risk management in overweight people and smokers; CB₁ receptor agonists in development for use in multiple sclerosis, Tourette’s syndrome, and dyskinesia in Parkinson’s disease²¹

2005 – CB₁ blockade with rimonabant, combined with a hypocaloric diet, found to promote significant weight decrease and waist circumference, and improvement in cardiovascular risk factors²²

Δ^9 -THC = delta⁹-tetrahydrocannabinol; GABA = γ -aminobutyric acid transaminase; IO-Lipids = Rimonabant In Obesity-Lipids; STRATUS-US = Studies with Rimonabant And Tobacco Use in the United States; RIO-Europe = Rimonabant In Obesity-Europe.

receptors. In animal models, endogenous cannabinoids have been shown to increase food intake when they bind to and activate CB₁ receptors.²⁷ Conversely, blocking or genetically knocking out the CB₁ receptor results in a decrease in food intake and a relative leanness.

The effects of stimulating the CB₁ receptor using dronabinol was shown in a study by Beal and cohorts²⁸ in which 139 patients with AIDS-related anorexia and ≥ 2.3 kg weight loss were randomized to receive either active drug or placebo. As shown in **Figure 1**, dronabinol was associated with increased appetite above baseline (38% vs 8% for placebo; $P = 0.015$). Weight was stable in dronabinol patients, whereas placebo recipients had a mean loss of 0.4 kg ($P = 0.14$). Of the dronabinol patients, 22% gained 2 or more kilograms, compared with 10.5% of those who received placebo, by the end of the 6-week study ($P = 0.11$).

CB₁ RECEPTORS AT THE CENTRAL LEVEL

The cannabinoid system in the central nervous system (CNS) has been implicated in appetite regulation by the respective hyperphagic actions of exogenous cannabinoids, such as delta⁹-tetrahydrocannabinol (Δ^9 -THC), and the

KEY POINT

When overactivated, the EC system triggers dyslipidemia, thrombotic and inflammatory states, and insulin resistance dysglycemia.

hypophagic effects of selective cannabinoid receptor antagonists. A study by Williams and Kirkham²⁷ demonstrated that the endogenous cannabinoid, anandamide, could induce overeating in rats in a dose-dependent manner by means of a specific action by central CB₁ receptors.

In another study by Jamshidi and Taylor,²⁹ presatiated rats that received intrahypothalamic doses of anandamide presented with significant hyperphagia. However, pretreatment with the selective CB₁ antagonist rimonabant 30 minutes prior to anandamide injection resulted in an attenuation of the anandamide-induced hyperphagia ($P < 0.001$), demonstrating that the CB₁ receptors can essentially be turned on or off at the central level, depend-

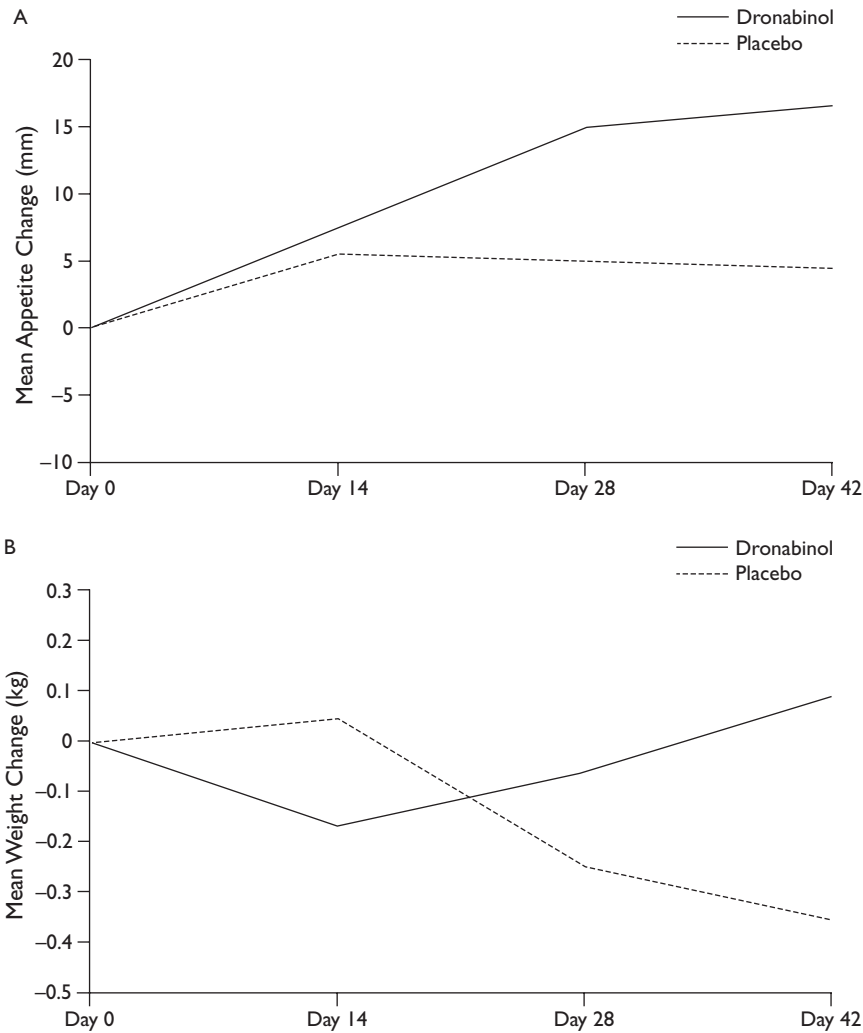


Figure 1. Effects of dronabinol on appetite and weight evaluated in 139 patients with AIDS-related anorexia or weight loss ≥ 2.3 kg. Reprinted with permission.²⁸

ing on whether they were exposed to a specific agonist or antagonist.

CB₁ RECEPTORS AT THE PERIPHERAL LEVEL

In addition to those found in the CNS, CB₁ receptors also occur at the level of the adipose tissue, or the fat cells. CB₁ receptors have also been located on nerve terminals that innervate the gastrointestinal tract,³⁰ which are believed to be involved in mediating satiety signals that originate in the gut and are independent of abdominal vagal nerve stimulation.³¹ A study by Gomez et al² showed that food deprivation in rats produced a 7-fold increase in anandamide content in the small intestine but not in the brain. Refeeding the animals normalized intestinal anandamide levels. Peripheral, but not central, ad-

ministration of anandamide resulted in hyperphagia in the rats, whereas peripheral, but not central, administration of rimonabant reduced food intake. Capsaicin deafferentation abolished the peripheral effects of both cannabinoid agonists and antagonists. This suggests that these agents modulate food intake by acting on CB₁ receptors located on capsaicin-sensitive sensory terminals. The results point to a role for peripheral CB₁ receptors in the regulation of feeding.²

A recent study by Engeli et al³² seems to support the presence of a peripheral EC system that is upregulated in human obesity. Data for this cross-sectional study were obtained from 20 lean and 20 obese postmenopausal women, as well as before and after a 5% weight loss in a second group of 17 obese women (**Figure 2**). Whereas

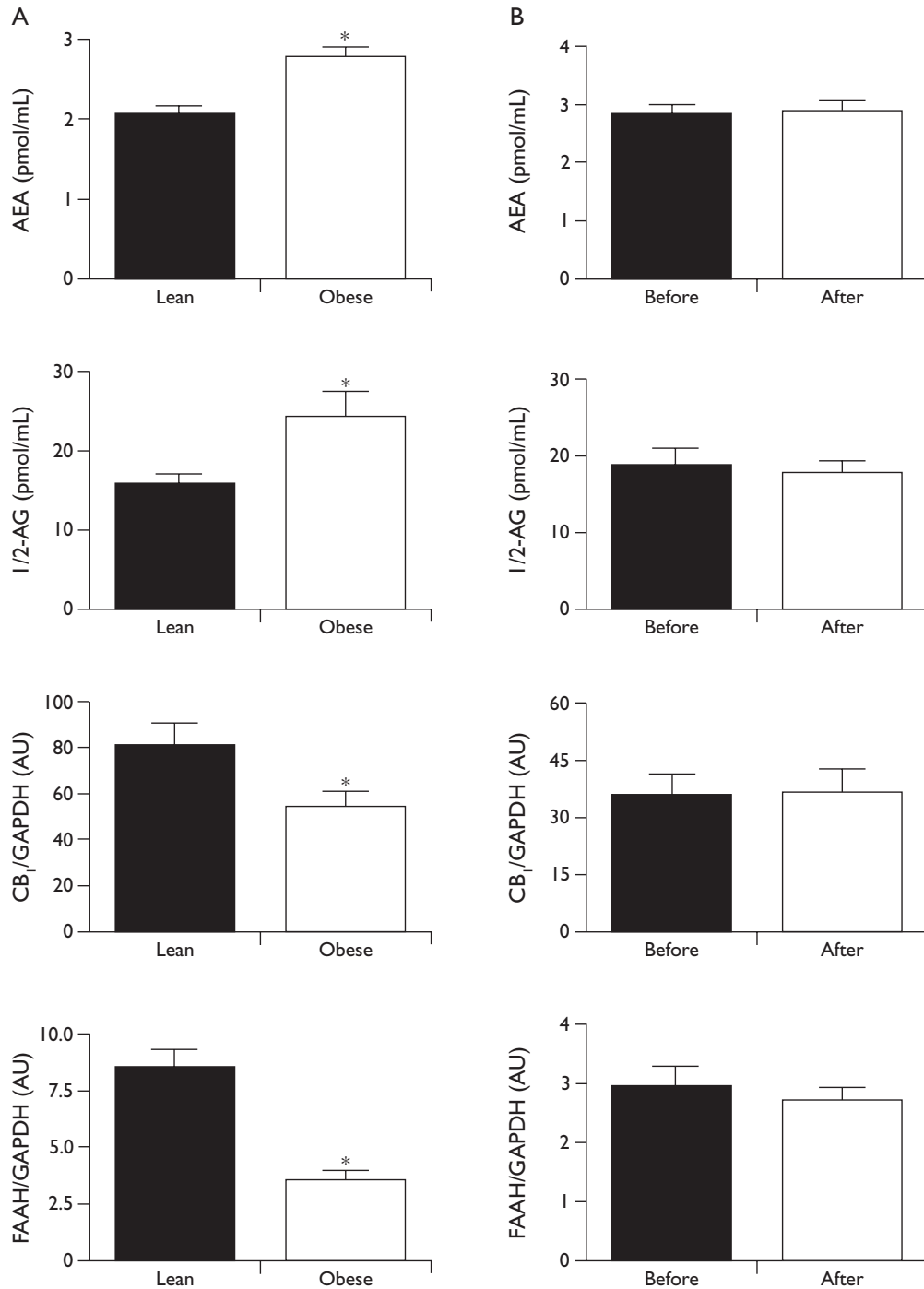


Figure 2. Influence of obesity and weight loss on the peripheral endocannabinoid system. Subcutaneous adipose tissue biopsies and blood samples were obtained from 20 lean and 20 obese postmenopausal women in a cross-sectional study (A) and from 17 obese postmenopausal women before and after a 5% body weight loss by a dietary protocol (B). Circulating levels of anandamide (AEA) and $1/2$ arachidonoylglycerol ($1/2$ -AG) were increased in the obese women by 35% and 52%, respectively. In contrast, adipose tissue cannabinoid (CB_1) messenger ribonucleic acid (mRNA) was decreased by -34% and fatty acid amide hydrolase (FAAH) mRNA by -59% in the obese subjects. Neither circulating levels of AEA and $1/2$ -AG nor adipose tissue CB_1 or FAAH mRNA were influenced by the weight loss protocol. Gene expression is given in arbitrary units (AUs), normalized by glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression. Group comparison was performed with Student's *t* test for independent samples (cross-sectional study) or the *t* test for paired samples (weight loss study). * $P < 0.05$ versus lean. Reprinted with permission.³²

circulating levels of anandamide and 1/2-arachidonoyl-glycerol increased by 35% and 52% in obese women compared with lean women ($P < 0.05$), adipose tissue messenger ribonucleic acid (mRNA) levels decreased by –34% for CB₁ and –59% for fatty acid amide hydrolase (FAAH) in obese subjects ($P < 0.05$). Neither circulating endocannabinoids and CB₁ nor FAAH expression were affected by a 5% weight loss.

THE ENDOCANNABINOID SYSTEM AND ADIPOSE TISSUE

Adipose tissue specializes in the storage and mobilization of fat. However, this tissue is an active endocrine organ that secretes a variety of factors in a manner that is dependent on its metabolic state.³³ Although different adipose depots are functionally distinct, visceral adipose tissue is most closely associated with the metabolic syndrome, which is a constellation of conditions that place people at high risk for coronary artery disease. These conditions include type 2 diabetes mellitus (DM), obesity, hypertension, having a poor lipid profile with elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and mild increases in low-density lipoprotein cholesterol—all of which are associated with insulin resistance.

Visceral adipose tissue, which is produced by subcutaneous as well as visceral fat, contains a number of proteins that have specific roles with respect to metabolism. Adiponectin is a large protein specifically expressed in adipocytes; its plasma levels correlate negatively with insulin resistance, coronary artery disease, and dyslipidemia in both mice and humans.³⁴ Tumor necrosis factor (TNF) is a cytokine that has been implicated in the pathogenesis of obesity and insulin resistance.³⁵ Adipose tissue expression of TNF is increased in obese rodents and humans; its presence is positively correlated with adiposity and insulin resistance. Thus, adipose tissue has the intrinsic ability to produce substances that, due to homeostasis, can increase or decrease its own mass as needed to store fat.

Hyperinsulinemia and insulin resistance are undergoing intense scrutiny as therapeutic targets in the treatment of obesity. Adiponectin expression in adipose tissue is decreased in animal and human models of obesity, and also in subjects with type 2 DM.^{36–39} One aspect of the study by Bensaïd et al⁵ examined the effect of rimonabant on hyperinsulinemia that characterizes obese rats. Daily treatments of rimonabant for 4 days induced a strong

KEY POINT

Visceral adipose tissue is most closely associated with the metabolic syndrome, which is a constellation of conditions that place people at high risk for coronary artery disease.

decrease in the plasma insulin rate (60%) in comparison to the insulin rate in control animals that received vehicle. However, rimonabant had no effect on plasma insulin levels in lean rats in this study. Although the mechanism is not fully understood, it is speculated that rimonabant stimulates mRNA expression of adiponectin (adipocyte complement-related protein, Acrp30), thus decreasing hyperinsulinemia, which may ultimately affect weight regulation.⁵

A study by Cote and colleagues⁴⁰ showed that visceral obesity, as measured by waist circumference, is associated with decreased adiponectin levels. Defining obesity as ≥ 30 kg/m², comparisons made among obese men with similar body mass index (BMI) values who markedly differed in their amount of visceral adipose tissue revealed significant differences in adiponectin levels (7.0 ± 3.0 $\mu\text{g/mL}$ for men with high visceral adipose vs 11.1 ± 4.0 $\mu\text{g/mL}$ for men with low visceral adipose; $P < 0.02$). Interestingly, when CB₁ receptors were blocked pharmacologically, fat accumulation was limited in the adipose cells and adiponectin production was boosted within the fat cells.⁵ Thus, these findings suggest that hormones implicated in lipid metabolism can be regulated. This regulation occurs first at the central level of the hypothalamus, which controls appetite and food intake. Regulation is theorized to occur at the peripheral level, by increasing metabolic activity and energy expenditure (**Figure 3**).⁵

High abdominal fat increases the risk for cardiovascular events. In a study by Pouliot et al,⁴¹ a group of obese men were compared to their lean controls with respect to a number of risk factors for cardiovascular disease.⁴² The results showed that obese men with high visceral fat accumulation had much higher levels of glucose intolerance, exhibiting increased insulin resistance with higher triglyceride levels and lower HDL cholesterol.

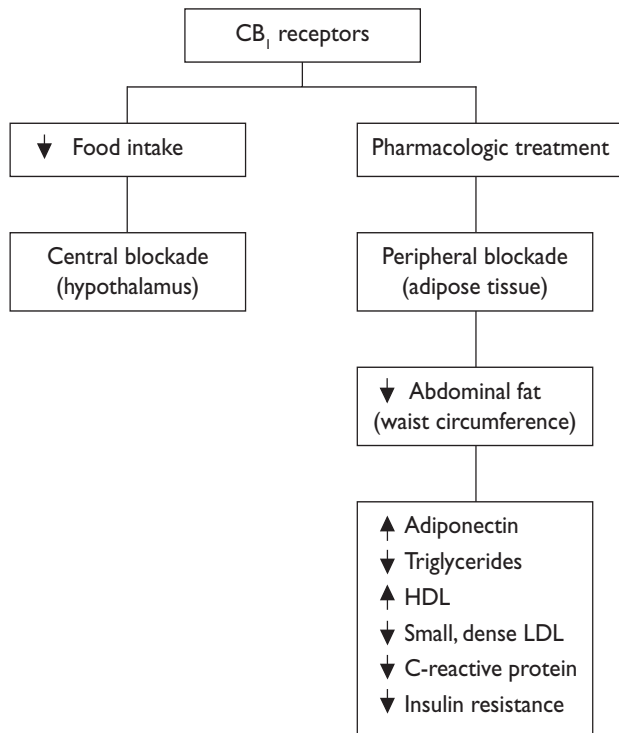


Figure 3. The effects of cannabinoid type I (CB₁) blockade on the metabolic syndrome. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

the development of the cardiovascular risk factors that define the metabolic syndrome; intra-abdominal fat may lead to diabetes, stroke, or other cardiovascular disease.⁴⁶

Although the presence of obesity (defined by increases in BMI) has increased significantly in the last 2 decades, obesity as measured by waist circumference has increased even more; 37% of men and 55% of women currently have high-risk waist circumferences, which place them at higher risk for cardiovascular disease even if their BMI is below 30 kg/m².⁴⁶ In the last 4 decades, the prevalence of abdominal obesity in the United States has tripled.⁴⁷ Thus, finding an EC antagonist that would block CB₁ receptors on the peripheral level may be useful in minimizing the risk of cardiovascular disease in people with increased waist circumference.

KEY POINT

With obesity typically measured as BMI, recent findings have shown that abdominal girth is a much better predictor of myocardial infarction than weight or BMI.

KEY POINT

High abdominal fat increases the risk for cardiovascular events.

WAIST CIRCUMFERENCE VERSUS BODY MASS INDEX AS A MARKER OF CARDIOVASCULAR RISK IN OBESITY

The recently published INTERHEART study showed that obesity is a major public health burden and the main risk factor for the development of cardiovascular disease, the leading global cause of mortality.⁴² With obesity typically measured as BMI, recent findings have shown that abdominal girth is a much better predictor of myocardial infarction than weight or BMI.⁴³ Thus, abdominal obesity can be easily measured by taking the waist circumference;⁴⁴ this measurement can serve as a crude indicator of intra-abdominal adiposity.⁴⁵ This hidden fat deep within the abdomen is one of the most significant contributors to

NEW THERAPEUTIC TARGET

The EC system and CB₁ receptor offer a new target for inducing weight loss and improving the metabolism of carbohydrates and lipids.^{48,49} In the Rimonabant in Obesity-Europe (RIO-Europe) study,⁵⁰ the new investigational drug rimonabant, which acts as a selective CB₁-receptor blockade, was shown to induce significant weight loss and to improve metabolic risk factors for diabetes and CVD in high-risk patients who are overweight or obese and have an atherogenic dyslipidemia.⁵¹

CONCLUSIONS

The EC system is an endogenous and physiologic system that plays a key role in the regulation of food intake and fat accumulation, as well as glucose and lipid metabolism. CB₁ receptors can be blocked both centrally and peripherally in the adipose tissue to help normalize an overactivated EC system. CB₁ blockade helps regulate food intake and adipose tissue metabolism, contributing to improved insulin sensitivity and other features of the metabolic syndrome. Targeting the EC system represents a new and exciting approach for the treatment of the most

prevalent cause of the cluster of abnormalities associated with the metabolic syndrome—visceral obesity.

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Dialogue Box

EDITORIAL BOARD

What causes overstimulation of the endocannabinoid (EC) system?

CANNON

The clinical drivers appear to be excess food intake and obesity. Obviously the two go together, but each of them seems individually to contribute to overstimulation of the EC system. Compounding the problem is the positive feedback loop that exists, which creates a vicious cycle. Overeating and obesity stimulate the EC system, which, in turn, stimulates the patient again to overeat and become more overweight, which further activates the EC system. Our challenge is to find a way to effectively interrupt the system.

EDITORIAL BOARD

What is the relationship of the EC system to marijuana?

CANNON

Marijuana is where research on the EC system began, when it was observed that marijuana users seemed to eat more. This observation led to the development of the exogenous cannabinoid (CB), Δ^9 -tetrahydrocannabinol (dronabinol), as a therapeutic agent for stimulating appetite in cachectic patients with AIDS and cancer. A number of studies then investigated the notion that blocking this action might be a way of treating obesity. What subsequently emerged was the discovery of a system that reminds me of the renin-angiotensin-aldosterone system, in that it acts at so many different levels. The EC system not only has central receptors in the hypothalamus, which affects the trigger and pleasure centers in the brain, but also peripheral receptors, which directly affect adipocytes. Acting through these and other receptors, the EC system is able to exert a significant effect on food intake and metabolic balance. I find it fascinating that the discovery of a huge new system in the body evolved from the simple observation that marijuana makes you eat more.

EDITORIAL BOARD

Since pleasurable emotional states are also induced in marijuana users, does the use of a CB antagonist like rimonabant cause unpleasant feelings?

CANNON

That does appear to occur in a small percentage of patients. My recollection is that 1% to 3% of patients treated with rimonabant develop some degree of depressed mood, although it is mild on testing. There are also another 2% to 3% of patients who feel anxious.

EDITORIAL BOARD

Clearly, stimulation of the CB₁ receptor causes an increased desire for food. Do elevated levels of C-reactive protein (CRP) and tumor necrosis factor and reduced levels of adiponectin arise from the increased food intake or from activation of the CB₁ receptor?

CANNON

It is probably a little bit of both. Studies have investigated changes in CRP and high-density lipoprotein cholesterol induced by CB antagonists and have tried to tease out the answer to that very question. In several of the rimonabant studies, it appears to be about half and half—half of the effect is due to weight loss, and the other half is otherwise unexplained and thus presumably related to the drug.

EDITORIAL BOARD

Based on animal studies evaluating the peripheral action of anandamide and rimonabant, it appears that there are CB receptors in the gut that affect food intake, independent of neurologic feedback to the hypothalamus. How would blockade of this receptor by rimonabant work?

CANNON

I believe the effect is related to reduced motility, causing a slowing down of the gastrointestinal tract. Such an effect would increase the feeling of satiety and hence produce a reduced food intake. Thus, blockade of the EC

Dialogue Box

system can cause a reduction in food intake by both central actions as well as peripheral actions at the gut level.

EDITORIAL BOARD

Would you care to speculate as to exactly how big a role the EC system plays in the causation of the metabolic syndrome?

CANNON

We are still far from being able to make a meaningful guess in that regard. However, it would not surprise me if some of the people who are showing up with the metabolic syndrome have an overactive EC system as the underlying cause.